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(71) Applicant 592220015
Masayasu Sugihara
Tokyo Women's Medical University Hospital Pharmaceutical department
8-1, Kawada-cho, Shinzyuku-ku, Tokyo
(71) Applicant: 592220026
Kenko Nkata
Tokyo Women's Medical University Hospital Pharmaceutical department
(71) Appicant: 000112912
Freund Industry Co.
2-14-2, Takadababa, Shinjyuku-ku, Tokyo
(74) Agent: Patent attorney, Yamato Tsutsui

(54) [Title of the Invention]

IMPROVEMENT METHOD OF ENTERIC COATING OF DRUG AND PHARMACEUTICAL COMPOSITION ACQUIRED THEREFROM

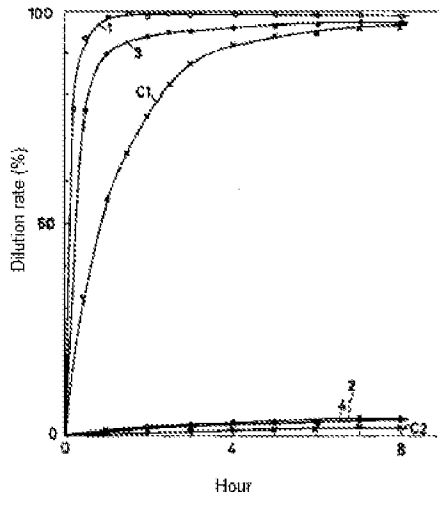
[Purpose]

To provide a technique to improve the enteric coating without increasing the water solubility of drugs with poor solubility in intestinal fluids

[Configuration]

The improvement method of enteric coating of drugs by means of dispersing the crystal grains of drugs with poor solubility in intestinal fluids in the air, and drying it after spraying and coating these crystal grains with an enteric polymer solution or dispersion fluid.

Fig. 3



[Scope of Claims for Patents]

[Claim 1]

An improvement method of enteric coating of drugs by means of disintegrating crystal grains of drugs with poor solubility in intestinal fluids in air, and drying it after spraying and coating these crystal grains with enteric polymer solution or dispersion fluid.

[Claim 2]

The improvement method of enteric coating of drugs according to Claim 1 by means of coating 0.2 − 20 parts by weight enteric polymer for 100 parts by weight crystal grains of drugs with poor solubility in intestinal fluids.

[Claim 3]

The improvement method of enteric coating of drugs according to Claim 1 and Claim 2 comprising of using crystal grains with particle size less than 50 μm.

[Claim 4]

A pharmaceutical composition with improved enteric coating obtained by means of the methods according to Claims 1, 2 and 3.

[Detailed Description of the Invention]

[0001]

[Industrial Applicability]

The present invention relates to the drug composition with the improved enteric coating, obtained by improving the solubility of intestinal fluids of crystalline drugs with poor solubility in intestinal fluids.

[0002]

[Conventional Technology]

Normally, drugs take orally by humans are dissolved in the digestive system and absorbed in the body in the form of a liquid. Therefore, if the drugs with a low solubility and slow dissolution rate (Hereafter, refer to as poorly water-soluble drugs) are taken orally, the entire drug is not dissolved in the body. Some part of the drug is excreted from the body without any effect.

[0003]

Therefore, not only is the drug wasted, but also the appropriate quantity of the drug cannot be determined since the absorbed quantity of drug varies with each individual and changes according to their digestive systems.

[0004]

Conventionally, there are large numbers of methods recommended to increase the solubility of poorly water-soluble drugs and to accelerate the dissolution rate in the digestive system. However, only few methods described below can be practically used.

[0005]

[1] An improvement method of enteric coating of drugs by means of disintegrating crystal grains of drugs with poor solubility in intestinal fluids in air, and drying it after spraying and coating these crystal grains with enteric polymer solution or dispersion fluid.

[0006]

[2] The improvement method of enteric coating of drugs according to Claim 1 by means of coating 0.2 − 20 parts by weight enteric polymer for 100 parts by weight crystal grains of drugs with poor solubility in intestinal fluids.

[0007]

[3] The improvement method of enteric coating of drugs according to Claim 1 and Claim 2 comprising of using crystal grains with particle size less than 50 μm.

[0008]

[4] A pharmaceutical composition with improved enteric coating obtained by means of the methods according to Claims 1, 2 and 3.

[0009]

However, the improvement methods of enteric coating of drugs are useful. However, the methods had the disadvantage of using a significant amount of additives in the drugs in order to achieve the desired goal.

[0010]

Further, in Japanese Patent No.1992-280402, the present inventor proposed the method of dispersing crystal grains of drugs with poor solubility in intestinal fluids in the air, and drying it after spraying and coating these crystal grains with an enteric polymer solution or dispersion fluid in order to improve the solubility of poorly water-soluble drugs by using a small amount of additives.

[0011]

[Problem to be Solved by the Invention]

The various methods described above are all designed to improve the water solubility of poorly water-soluble drugs. However, for example, in order to formulate the sustained release and enteric coating, it is necessary to improve the solubility of intestinal fluids of contained drugs. It is not required to improve the water solubility. However, in most cases, a method to control the water solubility is desired.

[0012]

Conventionally, based on this viewpoint, efforts to increase solubility of drugs were not attempted because it was thought that improvement in solubility could not be achieved.

[0013]

In the conventional method, the improvement of water solubility is attained by the inclusion of cyclodextrin and miniaturization or non-crystallization of crystalline drugs. (As opposed to the improvement in drugs readily soluble in intestinal fluids). It was recognized that a parallel relationship exists between intestinal fluid solubility and water solubility and they could not be treated differently.

[0014]

Further, the purpose of the present invention is to provide a technique to improve the enteric coating without increasing the water solubility of drugs with poor solubility in intestinal fluids.

[0015]

[Means for Solving the Problem]

It is useful for the formulation of enteric coating or sustained release if the enteric coating can be improved without increasing the water solubility of drugs with poor solubility in intestinal fluid. In case of enteric coating formulation, when the technique of invention of Japanese Patent No. 1992-280402 is applied for the enteric polymer, it is confirmed beneficial effects can be achieved.

[0016]

That is, the present invention provides the method of improving the enteric coating without increasing the water solubility of drugs by dispersing the crystal grains

of drugs with poor solubility in intestinal fluids in the air, and drying it after spraying and coating these crystal grains with an enteric polymer solution or dispersion fluid.
[0017]

Note that, the functional mechanism of the method of the present invention described above is not defined clearly as similar to the invention of Japanese Patent No. 1992-280402. However, the present inventor estimated a thin film of an enteric polymer solution coated on the crystalline surface of drugs and crystal grains can be soluble.
[0018]

The examples of drugs considered in the present invention method include, but are not limited to, non-pyrazolone analgesic antiphlogistine such as Aspirin, Ibuprofen, Indomethacin, Salicylic Acid, Diclofenac Sodium, Phenacetin, Phenylbutazone, Mefenamic Acid and Isosorbide Dinitrate, Nifedipine, Phenytoin Sodium, Noscapine, Carboquone, Ethinyl Estradiol, Prednisolone, Tolbutamide, Para-Aminosalicylic Acid, and Griseofulvin with low solubility or slow dissolution rate of intestinal fluids (digestive fluids exist in duodenum, small intestine, large intestine and the like; for example, fluids represented by Japanese Pharmacopoeia 2nd fluid). Note that, it is advisable to use the crystal grains with a particle size of 50 μm or less for the drugs considered in the method of the present invention.
[0019]

The examples of an enteric polymer include, but are not limited to, Carboxymethyl Cellulose (Product name "CMEC"), Hydroxypropyl Methylcellulose Phthalate (Product name "HPMCP"), Hydroxypropyl Methylcellulose Phthalate Acetate Succinate (Product name "HPMCAS"), Cellulose Acetate Phthalate (Product name "CAP"), Cellulose Acetate Trimellitate (Product name CAT), Polyvinyl Acetate Phthalate (Product name "VCAP"), various Methacrylate Copolymers and the like; however, any form of pharmaceutically allowed enteric polymers can be used.
[0020]

The examples of solvents include, but are not limited to, organic solvents such as methanol, ethanol, isopropanol, methylene chloride, hexane, acetone or combined solvents including more than 2 types of these solvents. Any solvent, in which an enteric polymer can be dissolved, can be used. In addition, the solubility of targeted crystalline drugs is not considered.
[0021]

Further, the enteric polymer used in the present invention can be used for spraying and coating, both as a solution or dispersion liquid such as emulsion. The representative of dispersion liquid includes, but is not limited to, Methacrylate Copolymer emulsion (Product name "Eudragit").
[0022]

The small amount of additives such as a surfactant, plasticizer, pH regulator and the like, can be added to the solution or dispersion liquid of an enteric polymer if required. In addition, the drugs similar to crystalline drugs, which are subject to solubility improvement, can be dissolved in these fluids. By doing this, a better solubility improvement can be achieved.
[0023]

Further, the percentage of crystalline drugs and dispersion liquid is set to 0.2 to 20% by weight. The percentage cannot be provided specifically since it depends on the

type of crystalline drugs and dispersion liquid. Generally, it can be set to 0.3 to 10% by weight. The most practical percentage is 0.5 to 5% by weight.

[0024]

If the percentage described above is less than 0.2% by weight, satisfactory solubility improvement cannot be achieved. On the other hand, even if the percentage of an enteric polymer is more than 20% by weight, the percentage of additives in drug formulation is increased without expecting any improvement in the solubility. Further, it is required to spray crystalline drug particles a number of times since spraying the particles only once does not generate sufficient coating on it. This makes the spraying process time longer and in turn disadvantageous.

[0025]

In the present invention, the spraying process should be performed when crystalline drug grains are dispersed in the air. For example, when using the tumbling granulator or the agitating granulator, if the spraying process is performed by exposing the grains, the grains adhere to each other and a nodule is formed. Satisfactory solubility improvement cannot be achieved because of non-uniform coating of an enteric polymer.

[0026]

The spraying process can be carried out when the crystalline drug particles are dispersed in the air by using suitable devices, such as a fluidized-bed with a spraying mechanism, flash dryer and the like. The nozzle in a concentric triplex structure (Japanese Patent No.1991-270598) is the suitable spraying mechanism in which the ejector of crystalline drug particles is set in the center and the ejector of an enteric polymer solution is set outside the center ejector. Furthermore, the ejector of compressed air is set outside of the enteric polymer ejector.

[0027]

Below, the present invention will be described in detail using the examples

[0028]

[Examples]

[Example 1 to 4]

Indomethacin particles (average particle size 10 μm) used as crystalline particles with poor solubility in intestinal fluid are sprayed with 2% by weight enteric polymer of various compositions as described in Table 1. The spraying process is carried out by using the structural jet coating device (Freund Industrial Co., Ltd., CM-MINI) as shown in Fig. 1 and by considering the conditions mentioned in Table 2.

[0029]

In Fig. 1, code 1 indicates processing room, 2 indicates cyclone, 3 indicates air induction part, 4 indicates filter, 5 indicates heater and 6 indicates blower. Drug particle 8, enteric polymer solution 9 and compressed air 10 are externally supplied to the 3-fluid spray nozzle 7 located at the base of the processing room. The particle introduction path 8a, the solution introduction path 9 and 2 types of the air introduction path 10a and 10b are set in the 3-fluid spray nozzle 7 as shown in the expanded Fig. 2. The drug particle 8 to be sprayed is contacted with the enteric polymer 9 by turning them in an upward direction from 3-fluid spray nozzle 7.

[0030]
Table 1

		Enteric polymer higher fatty acids solution (2% by weight density)		Enteric polymer higher fatty acids/Indomethacin weight ratio	Fluid	Remarks
		Enteric polymer higher fatty acids	Solvent			
Example	1	CMEC (*1)	Methylene chloride / ethanol =1 : 1	2%	2nd	
	2	CMEC (*1)	Methylene chloride / ethanol =1 : 1	2%	1st	
	3	HP-55 (*2)	Methylene chloride / ethanol =1 : 1	2%	2nd	
	4	HP-55 (*2)	Methylene chloride / ethanol =1 : 1	2%	1st	
Comparison	C1	————	————	————	2nd	indomethacin
	C2	————	————	————	1st	indomethacin

*1 CMEC (Freund Industrial Co., Ltd., Carboxymethylethylcellulose)
*2 HP-55 (Shinetsu Chemical Co., Ltd, Hydroxypropyl Methylcellulose Phthalate)

[0031]
Table 2

Introduced air temperature	40℃
Exhaust	4.0m^2/mim
Feeder air pressure	3. 2kg/cm^2G
Mist air pressure	1. 0kg/cm^2G
Supply of pharmaceutical particles	5g/mim
Supply of enteric polymer higher fatty acids solution	5g/mim

[0032]
Next, the dissolution curve shown in Fig. 3 was obtained by executing the dissolution test for drug composition of 6 mg of Example 1 to 4 and Comparative Examples C1, C2 provided in the method described above. In the dissolution test, the elution of Indometacin in each drug composition is evaluated with an automatic dissolution tester (DT-600 manufactured by Jasco International Co., Ltd.) by using 1st fluid and 2nd fluid, in conformity with Japanese Pharmacopoeia 12 dissolution test 2nd method (puddling).
[0033]
[Examples 5 to 8]
Mefenamic acid particles (average particle size 27 μm) used as crystalline particles with poor solubility in intestinal fluid, and the results of the testing similar to Examples 1 to 4 are shown in Fig. 4. Note that, the conditions were the same for Example 5 and Example 1, Example 6 and Example 2, Example 7 and example 3.

Comparative Example C3 was the same as Comparative example C1, and Comparative example C4 was the same as Comparative Example C2. However, the dilution test was performed with a 20mg sample for each of the tests.

[0034]

[Example 9 to 12]

Nifedipine particles (average particle size 9 μm) used as crystalline particles with poor solubility in intestinal fluid, and the results of the testing similar to Examples 1 to 4 are shown in Fig. 5. Note that, the conditions were the same for Example 9 and Example 1, Example 10 and Example 2, Example 11 and example 3, and Example 12 and example 4. Comparative Example C5 was the same as Comparative example C1, and Comparative example C6 was the same as Comparative Example C2. However, the dilution test was performed with a 90mg sample for each of the tests.

[0035]

[Effect of the Invention]

From the results of Examples 1 to 12 described above, it is experimentally-confirmed the enteric coating can be improved without increasing the water solubility of drugs with poor solubility in intestinal fluid.

[Brief Description of the Drawings]

Fig 1. is a configuration diagram showing the entire jet coating device used in the Examples

Fig. 2 is a cross-sectional view expanded to show the concentric triplex spray nozzle of the jet coating device shown in Fig. 1.

Fig. 3 is diagram showing the dilution curve of the pharmaceutical composition of Examples 1 to 4 and Comparative Examples C1 to C2.

Fig. 4 is diagram showing the dilution curve of the pharmaceutical composition of Examples 5 to 8 and Comparative Examples C3 to C4.

Fig. 5 is diagram showing the dilution curve of the pharmaceutical composition of Examples 9 to 12and Comparative Examples C5 to C6.

[Reference Numerals]

1. Processing room
2. Cyclone
3. Air induction part
4. Filter
5. Heater
6. Blower
7. Concentric triplex nozzle
8. Drug particles

8a. Particle introduction

9. Enteric polymer higher fatty acids solution

9a. Solution Introduction path

10. Compressed air

10a. Air introduction path

10b. Air introduction path

Translation of Drawings

Fig. 1

1. Processing room
2. Cyclone
3. Air induction part
4. Filter
5. Heater
6. Blower
7. Concentric triplex nozzle
8. Drug particles
9. Enteric polymer higher fatty acids solut
10. Compressed air

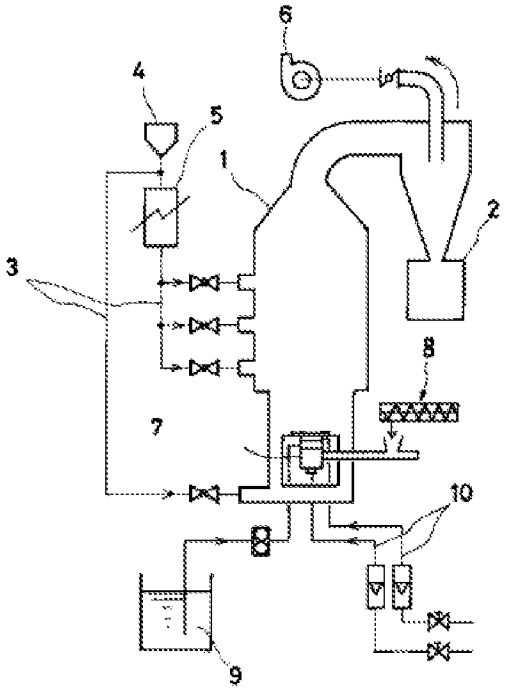


Fig. 2

8. Drug particle
9. Enteric polymer higher fatty acids solution
10. Compressed air

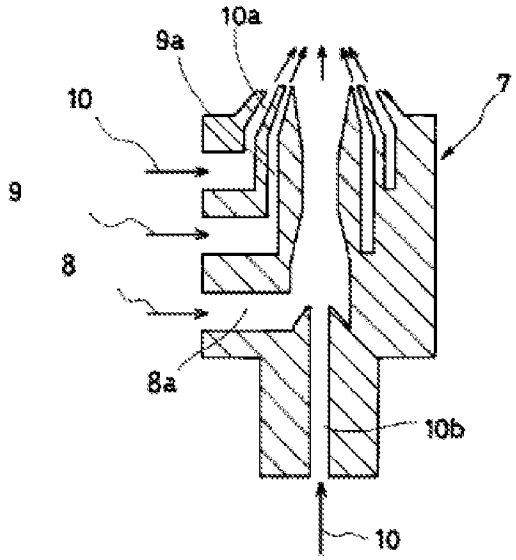


Fig. 3

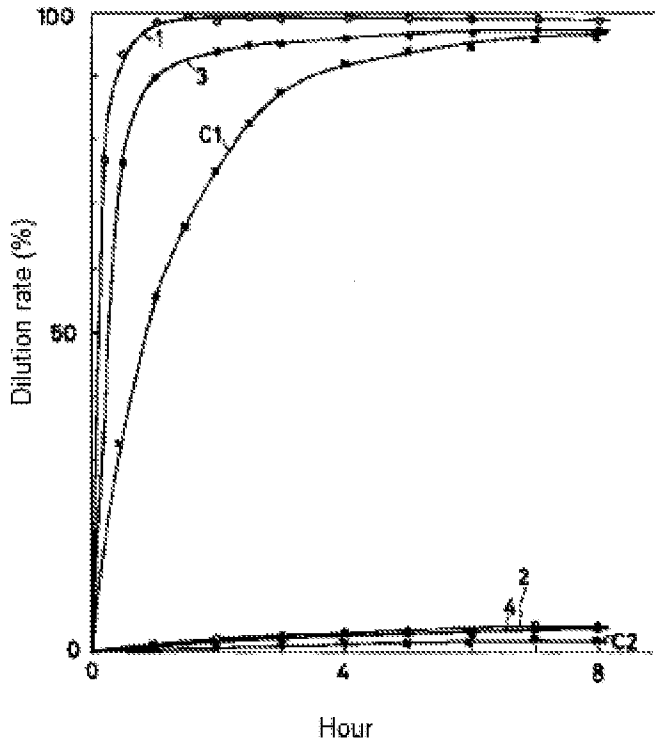

100
50
0
Dilution rate (%)
1
3
C1
2
4
C2
0
4
8
Hour

Fig. 4

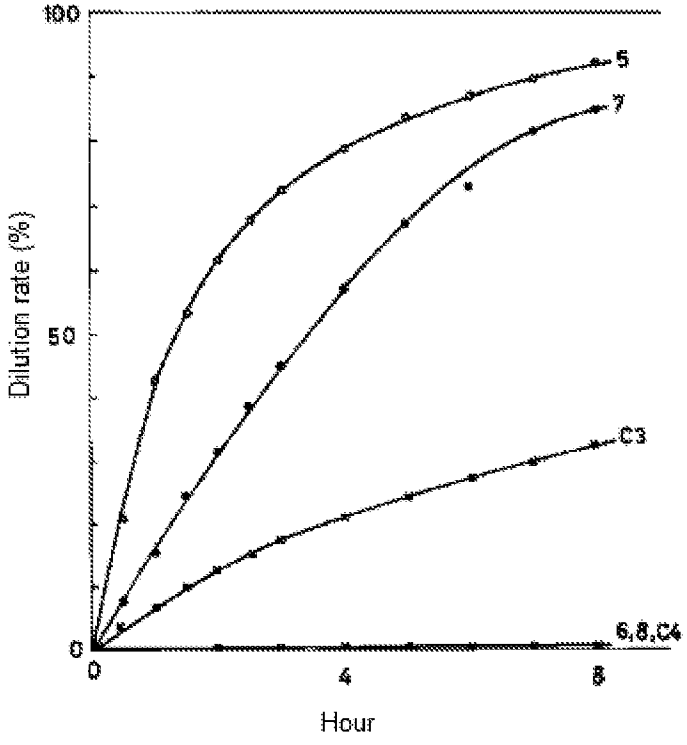
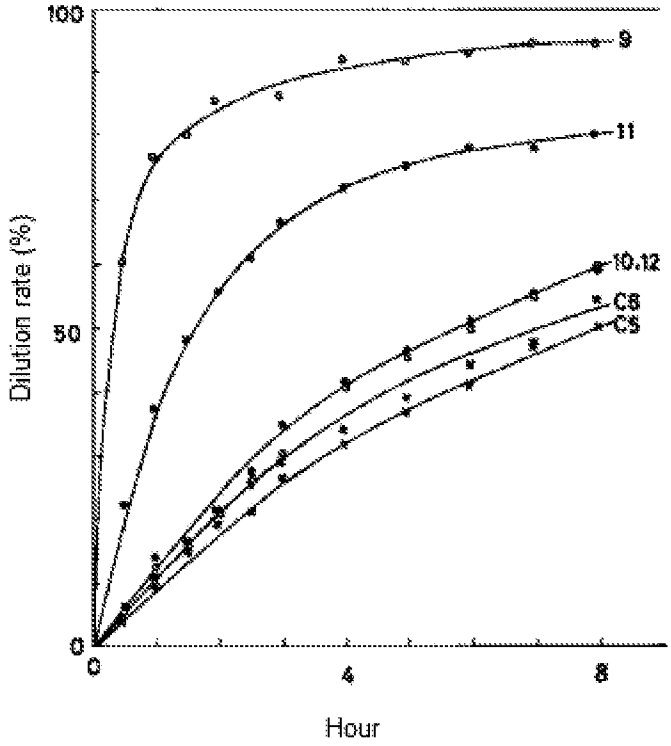

100
50
0
Dilution rate (%)
5
7
C3
6,8,C4
0
4
8
Hour

Fig. 5



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(72) Inventor: Sugihara Masayasu
8-1 Furuta-cho, Shinjuku-ku, Tokyo
Tokyo Woman's Medical University
Hospital c/o Pharmaceutical
Department
(72) Inventor: Nakata Kensuke
8-1 Furuta-cho, Shinjuku-ku, Tokyo
Tokyo Woman's Medical University
Hospital c/o Pharmaceutical
Department
(72) Inventor: Takei Seitsu
2-14-2 Takadababa Shinjuku-ku, Tokyo
c/o Freund Industrial Co., Ltd.
(72) Inventor: Unosawa Kazuomi
2-14-2 Takadababa Shinjuku-ku, Tokyo
c/o Freund Industrial Co., Ltd.
(72) Inventor: Yamanaka Kuniaki
2-14-2 Takadababa Shinjuku-ku, Tokyo
c/o Freund Industrial Co., Ltd.
(72) Inventor: Sugiyama Mamoru
2-14-2 Takadababa Shinjuku-ku, Tokyo
c/o Freund Industrial Co., Ltd.